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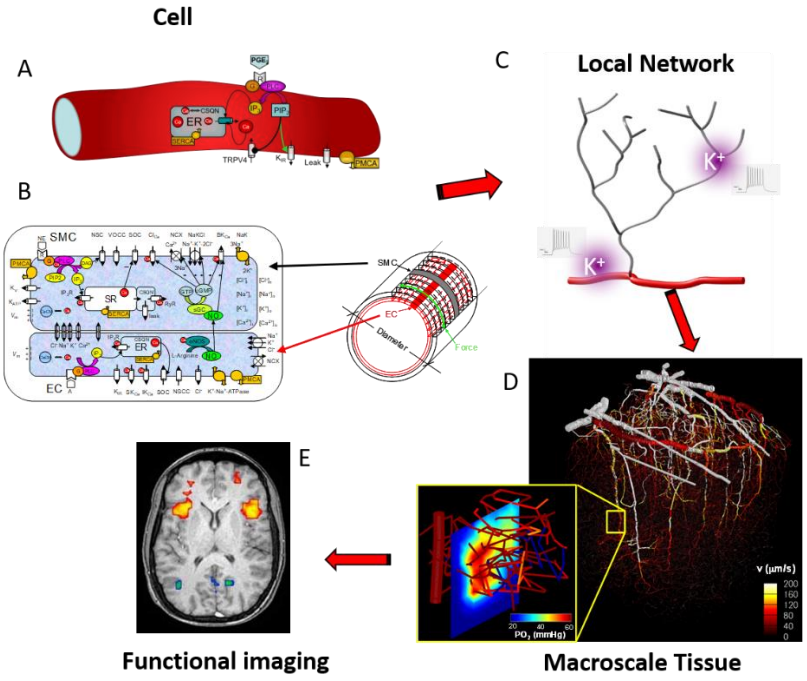
Abstract Text

Neurovascular Coupling (NVC) is a phenomenon that represents the relationship between neuronal activity and subsequent increase of blood flow to the region. This on-demand delivery of oxygen (O_2) and other nutrients is critical for proper functioning of the brain and its impairment is associated with pathological conditions including Alzheimer's disease, stroke and aging (Phillips, et al., *JCBFM,* 2016). The exact mechanism for NVC is not completely understood, but recent experimental evidence supports the idea that capillaries in the brain act as networks that sense neural activity, and initiate electrical signals that dilate upstream arterioles, causing an increase in local blood supply to the region of neural activity (Longden, et al., *Nature*, 2017).

In this study, we propose an integrative modeling approach to model microcirculatory responses to NVC mediators and their effect on the regulation of blood flow, tissue perfusion, and oxygenation. Single cell models of endothelial cells (ECs) and smooth muscle cells (SMCs) that captures membrane electrophysiology and Ca^{2+} dynamics are coupled through gap junctions to form branched capillary networks connected to PAs to examine capillary to arteriole communication. Hemodynamic responses are governed by conservation of flow, Fåhræus–Lindqvist effect, and the phase separation effect (Pries, Secomb, *AJPHAP,* 2005). Oxygen simulations provide PO_2 within vessels and in the tissue. Simulations are extended to a macroscale level by incorporating reconstructed brain vascular network data from (Blinder, et al., *Nature,* 2013).

The model predicts changes in tissue perfusion and oxygen distribution in response to neuronal activity. The model accounts for dynamic regulation of arteriolar diameters by NVC mediators and propagating electrical signals from connected capillary beds. Simulations suggest an important role of capillary-level NVC in regulating functional hyperemia. The theoretical framework presented allows for testing proposed NVC mechanisms and assisting in the interpretation of macroscale functional imaging responses in health and in disease.

Model code for the cell-level dynamics in ECs and SMCs are documented and maintained on the NSR Physiome Model Repository, while also being available upon request. Code that simulates the hemodynamics and tissue oxygen distribution will be uploaded on online repositories. Git version control is employed in order to maintain a history of changes to the model code, as well as allowing cleaner collaboration between contributors.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